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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,534	BROWN ET AL.	
	Examiner	Art Unit	
	GiGi Huang	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/4/2005, 3/9/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Specification

1. The use of the trademark Terramycin ® (oxytetracycline) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

2. The use of the trademark Aureomycin ® (chlortetracycline) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Non-Final Rejection

3. Claims 1-8 are present for examination at this time.

Claim Objections

4. Claims 2 and 3 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claims, or amend the claims to place the claims in

proper dependent form, or rewrite the claims in independent form. Claim 2, dependent from claim 1, is drawn to a formulation comprising a non-antibacterial amount of an antibacterial tetracycline. Claim 1 is drawn to a non-antibacterial tetracycline formulation which is a formulation comprising a non-antibacterial tetracycline, not a amount of an antibacterial tetracycline, thereby failing to draw from and limit the subject matter. Claim 3 is also objected to being dependent on claim 2 dependent on claim 1.

5. Claim 4 is objected to because of the following informalities: There is no period at the end of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for low doses of about 10 to about 60 milligrams of doxycycline, it does not reasonably provide enablement for non-antibacterial dose levels for the antibacterial tetracyclines as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation,

such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The claims are drawn to several types of antibacterial tetracyclines and which have entirely different efficacies, and methods of action on particular pathways. Thus, the claims taken together with the specification imply that all antibacterial tetracyclines will be as efficacious as doxycycline in the invention. However, that is not the case.

A prime example is the difference between doxycycline, minocycline, and oxytetracycline. The state of the prior art shows that doxycycline, minocycline, and oxytetracycline have different lipid solubilities and different chelating abilities and efficacies (see Glette et al. as an example of differences in function with leukocytes).

This makes some tetracyclines effective in some conditions but not others. Minocycline is traditionally used for dermatological conditions. Oxytetracycline, while possibly used for Chlamydia, or Lyme disease, is not the preferred choice. Doxycycline is the preferred choice due to improve pharmacological features such as absorption profile and efficacy. It is also the current prophylactic treatment for anthrax.

Amin et al. (Proceedings Natl. Acad. Sci.) teaches the use of minocycline and doxycycline in the treatment of nitric oxide synthase in osteoarthritis. Amin teaches that

the enzymes inhibited were especially susceptible and distinct to minocycline and doxycycline, showing that different tetracyclines have particular efficacies. Amin showed that there was inhibition of the macrophage iNOS, with minocycline greater than or equal to doxycycline, and OA-NOS where results with doxycycline were greater than for minocycline (Abstract).

This exemplifies the high unpredictability of the art and the high level of skill needed for those in the art.

The specification has provided guidance for the use of low doses of about 10 to about 60 milligrams of doxycycline.

However, the specification does not provide for the use of all antibacterial tetracyclines.

Considering the state of the art as discussed by the references above, particularly with regards to differences between the antibacterial tetracyclines, the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

9. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to administration of a non-antibacterial formulation that does not clearly state what the composition is comprised of and what the term non-antibacterial tetracycline is.

Claim 1 is also drawn to "an effective amount" which is also vague and indefinite as it is unclear what the effective amount is, thereby being anywhere from 0.01mg to 20,000mg or beyond.

Claim 1 is also drawn to tetracycline that can be both a genus and a species and there is no clear definition which embodiment is being utilized from the claim and those dependent from it.

Claim 1 is also drawn to administering a formulation for decreasing C-reactive protein "in need thereof" without defining a specific medical condition or patient population. This is vague and indefinite as C-reactive protein is a general marker for acute inflammation that can be elevated by arthritis, conjunctivitis, an allergic reaction, atherosclerosis, periodontal disease, and ear infection, or an infected cut.

By association one who is being treated for an ear infection or acne who inherently be lowering the inflammatory level and reducing the C-reactive protein. By not clearly defining a specific population, the claim 1 and all those that depend from it are indefinite.

10. Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 contains the trademark/trade names Terramycin ® and Aureomycin ®. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a specific tetracycline and, accordingly, the identification/description is indefinite.

It should be noted that the claim contains both the improper trademark and the generic tetracycline currently associated with it. This represents and improper Markush group since each species listed is to be distinct without multiplicity.

11. Claims 4-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4-8 are drawn to administration of a non-antibacterial tetracycline that does not clearly state what the term non-antibacterial tetracycline means.

The taken together with the specification imply that the chemically modified tetracyclines (CMT's) have **no** anti-bacterial activity *whatsoever.*

By applicant's own admission and taught in McNamara et al. (U.S. Pat. # 5,223,248), the prior art teaches that chemically modified tetracyclines exhibit substantially small or essentially no antimicrobial or anti-bacterial activity, meaning that there is *still* antimicrobial or anti-bacterial activity present.

There is no clarification in the claims or specification for the term other than chemically modified tetracyclines with "substantially" or "essentially" no antimicrobial activity, which still means there is still some antibacterial activity and inconsistent with the term "non-antibacterial". There is also no clarification or definition as to what degree of loss of antimicrobial or anti-bacterial activity is considered "substantially" or "essentially" as they are relative terms and are indefinite.

The term does no provide a standard or measure for ascertain the requisite degree, and one of ordinary skill in the art could not be reasonably apprised for the metes and bounds of the invention as the term is indefinite.

Claim Rejections - 35 USC § 102

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Amin et al. (Proceedings Natl. Acad. Sci.).

Amin et al. teaches the use of minocycline and doxycycline in the treatment of nitric oxide synthase in osteoarthritis. Overproduction of nitric oxide is involved in the pathogenesis of arthritis, angiogenesis, and other inflammatory diseases. Amin teaches

that the enzymes inhibited were especially susceptible and distinct to minocycline and doxycycline, showing that different tetracyclines have particular efficacies.

Amin showed that there was inhibition of the macrophage iNOS, where results with minocycline were greater than or equal to doxycycline, and in the case of OA-NOS, the results with doxycycline were greater than for minocycline.

There was a greater than 50% inhibition of nitric oxide synthase activity in the studies. This is significant because even modest effects (10-50%) of NOS inhibition in vivo can have profound affects on reduction of inflammatory events (Abstract, Page 14014, first column, second column, first and second paragraph, Page 14019, first column).

Since C-reactive protein is a measure of acute inflammation, an agent reducing the level of inflammation would inherently lower the level of C-reactive protein. Even current assays for c-reactive protein are know to be a general test, not a specific one since it measures the systemic level of inflammation. It can only reveal that there is inflammation in the body but not where it is. The high-sensitivity C-reactive protein assay also only indicates risk of heart disease but a positive test only indicates inflammation that can be due to birth control pills or inflammatory bowel disease (see Medline medical encyclopedia sheets).

Therefore, if you reduce the amount of nitric oxide synthase, which is a factor in inflammation, with tetracycline as taught by Amin in an inflammatory process, then the level of C-reactive protein will be inherently be reduced.

Amin et al. also patented these findings (U.S. Pat. # 5,789,395) teaching all of the above including method claims for administration in a mammal system, including maximum dosage ranges of about 0.1mg/kg/day to about 30mg/kg/day, but a dose in excess of about 50mg/kg/day would likely have side effects (Abstract, Col.4, lines 33-63, Col.5, lines 4-30, Col.6, lines 17-52, Col. 7, lines 1-5, 30-32, 58-68, Col. 8, lines 1-8, 42-67, Col. 11, lines 1-20, Col 17, lines 33-40, 57-68, Col. 18, lines 1-10, Claims 1-16).

All the critical elements are taught by the cited reference and thus the claims are anticipated.

13. Claims 1-4 rejected under 35 U.S.C. 102(b) as being anticipated by D'Agostino et al. (Journal of Infectious Diseases).

D'Agostino teaches the anti-inflammatory use and results of administering doxycycline for septic shock in vivo mouse models (Abstract).

D'Agostino taught the administration of doxycycline in mice after shock induction. The results showed reduction of nitrate (nitric oxide) that was correlated with protection. The survival rate was 20-80% dependent on the dose (0.3-7.5 mg/kg), but significantly higher than with lipopolysaccharide alone (given to prevent lethal septic shock) which was 10%.

This shows that doxycycline inhibits the release of inflammatory cytokines and nitrate (nitric oxide). It confirms that doxycycline acts mainly on the expression of inflammatory mediators. Large secretions of inflammatory mediators characterize severe sepsis and the ability of doxycycline to inhibit the release of nitrate together with

interleukin factors would explain its protective effect (Introduction 1st and 3rd paragraph, Materials and Methods 2nd- 4th paragraph, Results 1st paragraph, Discussion).

This intrinsic property of doxycycline to reduce of inflammatory cytokines and mediators would inherently reduce inflammation in the body and C-reactive protein levels.

All the critical elements are taught by the cited reference and thus the claims are anticipated.

14. Claims 1,4-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Ramamurthy et al. (U.S. Pat. # 5,827,840).

Ramamurthy et al. teaches a method for improving the healing response of epithelial tissue (e.g. skin, mucosa) due to acute traumatic injury in mammals. The method administers chemically modified tetracyclines (encompassing those in the claims) to improve the capacity of the tissue to heal acute would and decreases proteolytic (breakdown) activity in the tissue lowering collagenase and gelatinase (breakdown) activity (Abstract, Col. 1, lines 55-67, Col. 2, lines 1-5, Col.5, lines 8-27, Col. 6, lines 1-18).

Wound repair is essential as it is prone to bacterial infection if not reconstructed to form intact new tissue. There are several processes including inflammation in new tissue formation and remodeling of the tissue matrix (Col. 2, lines 40-54). The chemically modified tetracyclines have been found to inhibit excessive collagenolytic activity in vivo (Col.3, lines 6-14) and Ramamurthy stated the suggestion to use them in wound healing was made in U.S. Pat. # 4,704,383.

The maximal dosage to be administered to a subject of about 0.1mg/kg/day to about 30mg/kg/day, but a dose in excess of about 50mg/kg/day would likely have side effects, including humans. Both topical and systemic administrations are discussed (Col. 7, lines 7-38).

Examples and tests were done, resulting in evidence that the different CMT's inhibited collagenase and gelatinase at different efficacies but that there was inhibition of the two inflammatory mediators (matrix metalloproteinases/MMP's) collagenase and gelatinase.

This property of the CMT's to reduce of inflammatory cytokines and mediators would inherently reduce inflammation in the body and C-reactive protein levels.

All the critical elements are taught by the cited reference and thus the claims are anticipated.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

16. Claims 1,4-8 are rejected under 35 U.S.C. 102(e) as being anticipated by Levy et al. (U.S. Pat. Publication # 2004/0063674 A1).

Levy et al. teaches the use of tetracyclines to treat inflammatory process associated states. He teaches that inflammation is the body's reaction to injury and

infection. This releases many mediators and result in many serious clinical conditions including diabetes, arteriosclerosis, and atherosclerosis, among others (Abstract, Page 1, paragraph 1, 2, 5, 7and 10)

Levy teaches the protocol, theory, and the use of specific tetracycline compounds including CMT's in effective amounts, in the following inflammatory in vivo models: Lateral sclerosis, stoke, aortic aneurysms, diabetic complications, and arteriosclerosis. Levy also states that those skilled in the art would be able to ascertain many equivalents to the embodiments and methods described through routine experimentation.

Levy teaches that inflammation reduction through the use of tetracycline compounds in many diseases and disorders such as atherosclerosis, aneurysms, and osteoarthritis, can be explored and accomplished. Since C-reactive protein is a measure of inflammation, an agent reducing the level of inflammation would inherently lower the level of C-reactive protein (Page 2, paragraph 32, 34, 35, 40, Page 3, paragraph 45, Table 1, Page 5, paragraph 60, 61, 63, 65, Page 7, paragraph 80 and 85, Page 356, Example 9, Page 357, Examples 12-15, Page 358, Examples 17-19, Page 360, Example 24).

Even current assays for C-reactive protein are know to be a general test, not a specific one since it measures the systemic level of inflammation. It can only reveal that there is inflammation in the body but not where it is. The high-sensitivity C-reactive protein assay also only indicates risk of heart disease but a positive test only indicates

inflammation that can be due to birth control pills, inflammatory bowel disease, and many other conditions (see Medline medical encyclopedia sheets).

Therefore, if you reduce the amount of inflammation in the body with tetracycline as taught by Levy for an inflammatory process associated state (i.e. atherosclerosis, periodontitis, arthritis, Claims 1-119, especially 1-42), then inherently the level of C-reactive protein will be reduced.

All the critical elements are taught by the cited reference and thus the claims are anticipated.

Claim Rejections - 35 USC § 103

17. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kloppenburg et al. (Immunopharmacology).

Kloppenburg et al. teaches the use of minocycline in the reduction inflammation of rheumatoid arthritis.

Kloppenburg also teaches that the used of minocycline (100mg twice a day) reduced serum level of intereukin-6 and C-reactive protein (CRP). There appears to by a positive correlation between IL-6 and CRP levels. The randomized controlled trial revealed superior anti-inflammatory effects of the minocycline verses the placebo group. The effect on the acute phase response by the minocycline serve to contribute that minocycline modulates the synovial inflammation in patients with rheumatoid arthritis (Abstract, Page 166, paragraph 3.2.2, paragraph 3.2.3, Table 3, Page 167, paragraph 4, Page 168).

Kloppenburg et al. does not expressly teach the use of doxycycline.

Golub et al. (U.S. Pat. # 4,666,897) teaches the use of several species of tetracyclines for the inhibition of matrix metalloproteinase activity due to their anti-inflammatory properties (see Plewig et al, Anti-Inflammatory Effects of Antimicrobial Agents: An In Vivo Study, for well documented anti-inflammatory properties of the tetracycline class).

Golub teaches that administration of minocycline in synovial tissue with rheumatoid arthritis among several examples (Col. 12, Example 12). The minocycline reduced the level of collagenolytic enzyme activity (MMP's and thereby inflammation) by 69-82%, which was very significant (Col.13, lines 12-25). Golub envisioned in the description of preferred embodiments, the use of doxycycline (listed with tradenames) for use in the invention (Abstract, Col. 2, lines 22-60, Col.7, Table 1-2, lines 56-55, Col.8. lines, 23-35, Col. 12, Example VI, Col. 13, lines 1-40).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use doxycycline and other tetracyclines, as suggested by Golub, and produce the instant invention as it is known that different tetracycline species have different efficacies and it would be obvious to try several similar species (e.g. doxycycline) to find ones that would have the highest efficacy (Col.3, lines 7-17).

One of ordinary skill in the art would have been motivated to do this because it would not be cost effective to produce and bring a product to market that did not have the optimum or desirable degree of efficacy.

All the critical elements are taught by the cited reference and thus the claims are anticipated.

Conclusion

18. Claims 1-8 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GiGi Huang whose telephone number is (571) 272-9073. The examiner can normally be reached on Monday-Friday 7:30AM-5:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GH

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SUPERVISORY PATENT EXAMINER